

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
16 May 2002 (16.05.2002)

PCT

(10) International Publication Number  
**WO 02/38123 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 7/48**,  
31/201, 31/202, 31/07, 47/36, A61P 17/00

(21) International Application Number: PCT/NO01/00437

(22) International Filing Date:  
1 November 2001 (01.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
20005718 13 November 2000 (13.11.2000) NO

(71) Applicant (*for all designated States except US*): **WAD-  
LUND AS** [NO/NO]; c/o Wadstein, Hegdehaugsveien 23,  
N-0352 Oslo (NO).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **WADSTEIN, Jan**  
[SE/NO]; Hegdehaugsveien 23, N-0352 Oslo (NO).

(74) Agent: **OSLO PATENTKONTOR AS**; Postboks 7007 M,  
N-0306 Oslo (NO).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AT  
(utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA,  
CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE  
(utility model), DK, DK (utility model), DM, DZ, EC, EE,  
EE (utility model), ES, FI, FI (utility model), GB, GD, GE,  
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,  
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,  
MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU,  
SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR,  
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,  
TG).

**Declaration under Rule 4.17:**

— *of inventorship (Rule 4.17(iv)) for US only*

**Published:**

— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*



**WO 02/38123 A1**

(54) Title: A SKIN CREAM COMPOSITION

(57) Abstract: The present invention is related to compositions containing chitosan conjugated CLA (conjugated linoleic acid) and a chitosan conjugated Vitamin A or a  $\beta$ -cyclodextrin conjugated vitamin A. The invention also concerns the preparation of the compositions. The compositions according to the invention can be used as topical and cosmetic compositions as well as pharmaceutical compositions for treatment of atopic dermatitis, psoriasis eczema as well as eczema of different origins and solar dermatitis.

## Skin Compositions

**Field of the invention**

The present invention relates to compositions, as given in  
5 claim 1, for application to (human and animal) skin and  
their use for improving the conditions and the appearance  
of skin. More particularly, it relates to novel skin  
creams, ointments, gels, salves, balms and solutions  
containing chitosan conjugated CLA (conjugated linoleic  
10 acid) and chitosan conjugated or  $\beta$ -cyclodextrin conjugated  
vitamin A for topical treatment of the skin structure. The  
invention also concerns the preparation of the compositions  
according to the invention as given in claim 18. The  
compositions according to the invention can be used for  
15 preparation of topical, cosmetic and pharmaceutical  
compositions as given in claims 19, 20 and 21,  
respectively. The prepared pharmaceutical compositions can  
be used for treatment of atypical dermatitis, psoriasis  
eczema as well as eczema of different origins and solar  
20 dermatitis as given in claim 22. Furthermore, the  
compositions according to the invention can be used to  
improve the skin thickness and elasticity as given in claim  
23. The invention does also concern a method for improving  
skin thickness and skin elasticity as given in claim 24.  
25

**Background of the invention**

Skin creams of different kinds have been more and more  
popular and a lot of cosmetic companies are producing  
"miracle" creams. Scientists are quite aware of the  
30 necessity to "feed" the skin in different ways. Except from  
moistening factors, the skin needs also, as the whole body,  
nutrients as for instance vitamins, minerals, calories etc.

A number of new ointments or creams is introduced to the  
35 market each year, containing new agents believed to be good  
for the skin. However, it has been shown lately as reported  
in The Time (August 28, 2000, pp. 34-38. *Facelift in a  
jar.*) that a number of these creams contains questionable

ingredients and in amounts not meeting the amounts on the package leaflets.

The skin is the biggest organ of the human body and is very complex, due to its many functions. It should prevent the body from poisoning substances, which means it must have a strong barrier function. It should be able to sustain trauma of different kinds and if the skin is damaged it must be able to quickly repair itself. However, the skin is also sensitive to different factors such as, e.g., sun radiation which causes ageing of the skin. Many creams are on the market to protect against sunshine and others to reduce ageing of the skin, and a lot of research have been put into the fields of skin protection, skin reparation and anti-ageing.

Compounds that can feed the skin are fatty acids. Among them there is one recently discovered fatty acid called CLA (conjugated linoleic acid). The term CLA is a generic term used to reference both conjugated linoleic acid and conjugated linolenic acid. Since linoleic acid is an essential fatty acid, its conjugated forms are readily absorbed into lipids and fats. Theoretically, conversion of ordinary linoleic acid to conjugated linoleic acid results in eight isomers.

CLA is known to have several effects on different cell systems. In the body effects such as antioxidant effect, immune stimulant effect and antiallergenic effects are observed. Additionally CLA has been shown to promote cell generation in both animal and human subjects. It does also have effect on fat reduction and muscle building. For skin CLA could be an ideal substance to improve skin quality. However, due to its nature the major problem is to make it penetrate the skin and exert its effects directly in the skin.

Another nutrient is A-vitamin acid which has a well-documented effect on skin. In the cells A-vitamin acid has nutritional effects and promotes regeneration. However, this compound does also have side effects. Due to its irritant effect it can only be bought on prescription, and is used in certain skin diseases as acne, psoriasis, eczema and others. It is known that the fat-soluble vitamin A is harmless to the skin, and inert, but if it penetrates the skin cells it will immediately be hydrolysed to A-vitamin acid and can exert its beneficial effect without irritation. It has earlier been shown by Wadstein (1991) that vitamin A bound to a certain carrier ( $\beta$ -cyklodextrin) could penetrate the skin almost as effective as A-vitamin acid, but without the above mentioned side effects. Creams with this solution has successfully been sold for more than 10 years.

Bovien colostrum does also have a beneficial effect on the skin and can therefor be added to skin compositions. Colostrum concentrates normally contain IgG (gammaglobulin) which enhances fagocytosis; IgA which protects the mucosal surfaces; IgM which also enhance fagocytosis and is especially effective against micro-organisms; IgD which stimulates B-cells to produce antibodies and IgE which is associated with allergic reactions. Another important factor found in bovine colostrum is IGF-1 (growth factor) which is an important promoter of cell formation and promotes skin juvenation in skin compositions. The antibacterial effects of the immunoglobulins have a certain impact on the healing efficacy of the skin compositions, as it has been shown that bacterial infection occurs in 100% of eczema's and skin wounds.

Dryness of the skin is an other problem. Several substances (hydrogels) such as, for example, chitosan, carboxy methyl cellulose, cyclodextrins have been used to prevent this.

Chitosan is a deacetylated breakdown product of chitin which is one of the most abundant polymers in the nature after cellulose. Chitosan is prepared from chitin which for example may be produced from the waste in the shellfish industry where shrimps are processed. Chitin and chitosan both belong to the group of polysaccharides.

Chitosan has the properties of a gel and binds as such water and contributes to the moistening effect of the skin. As dryness of the skin is a major problem, the ability to bind water both treat and prevent this condition. Chitosan does also have an anti-microbial effect beginning at a concentration of about 0.4 wt% and upwards of the composition.

From the prior art several topical formulations for treatment of the skin comprising conjugated linoleic acid are known. WO-9932105 discloses a composition for topical use comprising CLA esters and a topical carrier. US-6019990 discloses cosmetic formulations comprising a conjugated linoleic acid and an ester of conjugated linoleic acid. These formulations may also contain a UV absorbing compound. WO-0037040 describes a topical composition comprising (a) conjugated linoleic acid, and/or derivatives thereof comprising conjugated linoleic acid moieties, in which at least 50% by weight of the conjugated linoleic acid and/or moieties, is present as the cis 9 trans 11 and (b) a dermatologically acceptable carrier.

Also cosmetic preparations containing chitosan are known for example from US-5057542 and Pittermann W. et al., *Efficiency of high molecular weight chitosan in skin care applications* in Chitin Handbook, R.A.A. Muzzarelli and M.G. Peter, eds., European Chitin Society, 1997.

Additionally cosmetic compositions containing both chitosan and linoleic acid are known from EP-A-414608, which discloses cosmetic compositions comprising chitosan, some



glucosamine and at least one organic acid selected from gluconic acid and succinic acid. FR-2785179 describes cosmetic compositions containing a aqueous dispersion of particulate filmogenic polymers and a polyorganosiloxane polyester of the type dimethicone copolyol comprising ester groups derived from fatty acids of vegetable oils comprising mainly oleic acid. WO-9847487 discloses a drug delivery system containing a liquid crystalline phase and a reverse micellar liquid crystalline phase. US-5874463 describes a hydroxy-kojic acid skin peel for treatment of hyperpigmentation, melasma, dyschromia, rhytides, photodamage and aging. And WO-9939700 discloses pharmaceutical compositions in form of nanoparticles comprising a composite material, consisting of at least one lipidic substance and of at least one amphiphilic substance and of a pharmaceutically active principle.

#### Summary of the invention

Contrary to the present invention none of the above publications are related to chitosan conjugated CLA compositions. The CLA skin compositions of the present invention are based on sophisticated research by combining scientific results from quite different areas, and the characteristic features of these skin compositions are the content of biological active components which can provide the skin with necessary nutrients.

The present invention has solved the problem of CLA's insufficient skin penetration by conjugating CLA with chitosan. In the chitosan conjugated CLA complex chitosan works as carrier that enables CLA to reach into the stratum corneum of the skin.

In a first aspect of the present invention there is provided a composition containing chitosan conjugated CLA (conjugated linoleic acid) and a chitosan conjugated Vitamin A or a  $\beta$ -cyclodextrin conjugated vitamin A, where the content of CLA is 0.1-99 wt%, the content of chitosan

is 0.025-25 wt%, and the content of Vitamin A is 0.025-10 wt%.

Optionally the compositions can contain chitosan conjugated  
5 vitamin E as well as sun protective factor and/or bovien colostrum concentrate.

Optionally lactose can be included in certain compositions of the present invention for treatments where it is  
10 important to promote the growth of the natural occurring acidofilic bacteria's as in eczema's or wounded skin. Lactose is a carbohydrate that exhibit different effects such as promotion of absorption of calcium and other minerals and promotion of growth of acidofilic bacteria's.

15 Additionally the compositions of the present invention may contain ingredients and adjuvants commonly used in the art to prepare skin care compositions, for example anti-oxidants such as, e.g., tocopheryl acetate and tocopherol;  
20 conservation agents such as, e.g., methyl-p-hydroxybenzoate and acetyl-p-oxybenzoate; emulsifiers such as, e.g., Emulgator E 471 and E 472 c; fillers such as, e.g., olive oil, arachidis oleum, oleum soya, stearin, water; hydrogels such as triethanolamine, carboxy methyl cellulose, chitosan  
25 and resin.

Chitosan is also preferable due to its antibacterial effect which means that it is able to preserve the composition in addition to provide an antibacterial effect on the skin  
30 surface.

However, the unique property of chitosan to bind fat can also be used to bind other important nutrients such as A- and E-vitamins and to promote transport / increase  
35 penetration into the skin (See Pittermann W. et al., *Efficiency of high molecular weight chitosan in skin care applications* in Chitin Handbook, R.A.A. Muzzarelli and M.G. Peter, eds., European Chitin Society. 1997). The

compositions of the present invention contain chitosan conjugated vitamin A or  $\beta$ -cyclodextrin conjugated A vitamin and optionally chitosan conjugated vitamin E. As mentioned above  $\beta$ -cyclodextrin, belonging to the polysaccharide group, can be used as a carrier but in our opinion chitosan is superior in this respect.

The chitosan conjugated vitamin E has two effects. Firstly, vitamin E, as an antioxidant, protects the oxidation of CLA and secondly, it has an antioxidant effect on the skin.

To regulate the pH of the compositions weak acids, normally used in compositions for application to the skin, can be used such as lactic acid. Lactic acid belongs to the AHA series of natural acids, but has less irritating effects than fruit acids. Also bicarbonate solutions such as sodium bicarbonate may be used to adjust the pH of the compositions. The pH of the compositions are adjusted to a pH between 2 and 8, preferably 5.5 which is an ideal acidity for active skincare.

As several of the ingredients are sensitive to sun radiation a sun screen may optionally be added. A sun protective factor of 1-30 is well suited, preferably a sun protective factor of 4 is used. The sun screen does give a protection both to the composition and the skin during the time when the composition is supposed to penetrate the skin surface.

In summary, these compositions are unique in the sense that they combine several active ingredients, which has previously not been possible.

#### Detailed description of the invention

CLA (conjugated linoleic acid)

The CLA isomers of most interest in the present invention are cis-9-trans-11-linoleic acid (c9t11) and trans-10-cis-12-linoleic acid (t10c12). These isomers are commonly known



to give physiological benefits and are also easily prepared from natural sources. The CLA should preferably have 0.1 - 90% of each isomer, preferably in a 50:50 relation.

Some suitable substances having the above mentioned characteristics are: CLA 80 (Tonalin), CLA isomer c9t11 and CLA 80 isomer t10c12, which contain equal amounts of the two isomers, namely about 34,5% of each.

The amount of CLA in the composition in the form of chitosan conjugated CLA should be in the range of 0.1 wt% to 99 wt% of the composition, preferably 0.5 wt% to 70 wt% and most preferred 0.8 wt% to 40 wt%.

#### Chitosan

The degree of deacetylation is important for the properties of chitosan as is the molecular weight of the polymer. The percent of deacetylation in the chitosan used in the present compositions should be in the range of 70 to 95%, preferable 87-90%, while the preferred molecular weight of the chitosan used in this invention should be in the range of 5,000 to 50,000. The viscosity of the chitosan polymer itself should be in the range of 120 - 169 mPa's, preferably about 140 mPa's, determined in 1% acetic acid at 25°C, with a concentration of 1% chitosan (dry weight basis). One suitable substance having the above mentioned characteristics is Chitosan Biopolymer L112.

The amount of chitosan in the composition in the form of chitosan conjugated CLA and chitosan conjugated vitamin A should be in the range of 0.025 wt% to 25 wt% of the composition, preferably 0.1 wt% to 16 wt% and most preferred 0.5 wt% to 10 wt%.

#### Vitamin A

The compositions should contain vitamin A in an amount between 0.025 wt% to 10 wt%.

Bovien colostrum

A bovien colostrum concentrate should preferably contain the following immunoglobulins in the given amounts:

Immunoglobulin	Amount of total antibody content
IgG	70-85%
IgA	about 15%
IgM	5-10%
IgD	0.2%
IgE	0.002%

5

Additionally the concentrate should contain IGF-1 in a concentration of about 250 ng/kg colostrum concentrate.

10 One suitable colostrum concentrate comprising 60% pure immunoglobulins in the relative amounts described above is produced by Kemikalia AB, Lund, Sweden.

The amount of freeze-dried bovine colostrum powder (with the above content) included in the composition should be from 0.5 g up to 10 g per 100 g of the composition.

15

Chitosan conjugated CLA

The ratio of CLA to chitosan in the chitosan conjugated CLA complex may be in the range of 25 : 1 to 1 : 2.

20 The preferred ratio of CLA (mixture with cis-9-trans-11-linoleic acid (c9t11) and trans-10-cis-12-linoleic acid (t10c12) in equivalent concentrations of the isomers) to chitosan in the chitosan conjugated CLA complex is about 4:1.

25

Chitosan conjugated vitamin A

30 The amount of chitosan conjugated vitamin A in the compositions should be in the range of 0.1 wt% to 50 wt% of the composition (i.e. about 2,000 - 45,000 IU). The ratio between chitosan and vitamin A in the chitosan conjugated vitamin A should be in the range of 1:25 to 1:1.

Preparation of chitosan conjugated CLA

To achieve a satisfactory conjugate the chitosan conjugated CLA should be prepared by heating CLA with chitosan at 70°C with stirring for about half an hour. The complex formed is then allowed to slowly cooled to about 50°C.

Preparation of chitosan conjugated vitamin A

To achieve a satisfactory conjugate the chitosan conjugated vitamin A should be prepared by heating A-vitamin palmitate together with chitosan at 55°C with stirring for about half an hour. The complex is subsequently cooled to 50°C.

Preparation of chitosan conjugated vitamin E

To achieve a satisfactory conjugate the chitosan conjugated vitamin E should be prepared by heating, e.g., E-vitamin palmitate together with chitosan at 55°C with stirring for about half an hour. The complex is subsequently cooled to 50°C.

Preferred embodiment

The preferred conjugation ratio of CLA (mixture with cis-9-trans-11-linoleic acid (c9t11) and trans-10-cis-12-linoleic acid (t10c12) in equivalent concentrations of the isomers) to chitosan is 4:1.

By conjugating the CLA with Chitosan (complex binding) this new conjugate is believed to be one ideally suited part of a new skin composition. Another is  $\beta$ -cyclodextrin conjugated vitamin A or chitosan conjugated vitamin A and together with bovine colostrum we have optimised the skin composition with regard to anti-ageing capacity, rejuvenating ability and moistening effect on the skin in deeper layers. Added should of course be vitamin E and sun protection factors which have 2 effects: 1) to protect the skin cream from oxidation and 2) protect the skin.

Additionally, the compositions also promotes the growth of natural skin acidophilus bacteria's and natural symbiotic skin flora.

- 5 The compositions according to the present invention can also be used for treatment of atypical dermatitis, psoriasis eczema as well as eczema of different origins and solar dermatitis.
- 10 The compositions according to the present invention can be used to prepare topical, cosmetic and pharmaceutical compositions depending on the adjuvants and other components added.
- 15 Furthermore, the compositions of the invention can be used to improve skin thickness and elasticity.

The invention also provides a method for improving the skin thickness and the skin elasticity. The method comprises  
20 application of a sufficient amount of a composition according to the invention on the skin of a human or animal subject.

The dosage will depend on the nature of the conditions  
25 being treated, and possible associated treatments. The daily dosage of the compositions will range from 0.5 to 10 g in one or more administrations.

The following examples illustrate the invention but do not  
30 limit it in any way.

### **Experimental part**

#### **Example 1 Preparation of CLA-Chitosan skin cream**

35 The properties of the cream depends on CLA's join action with chitosan. To achieve a satisfactory conjugation between the active components the cream should be prepared as described below:

100 gram CLA 80 (Natural AS Oslo) is heated with 30 g Chitosan, Biopolymer L112 (Natural, Oslo) to 70°C with stirring for about half an hour. The complex which is  
5 formed is then allowed to slowly cool to 50°C.  
20 g A-vitamin palmitate (Roche) is heated to 55°C together with 10 g Chitosan, Biopolymer L 112 (Natural,Oslo) with stirring for about half an hour. The complex is subsequently cooled to 50°C, and is then mixed into a cream  
10 base of standard type, heated to 50°C, together with the CLA-chitosan-complex of 50°C in such a way that the total amount of CLA is 2 g, A-vitamin palmitate 0.2 g and the total amount of chitosan is 0.7 g.  
The pH of the newly formed solution is adjusted with  
15 lactate or sodium bicarbonate to pH 5.0-5.5.

The additional ingredients are 1 wt% tocopheryl acetate and 0.2 wt% tocopherol as anti-oxidants.

20 In the final formulation sunscreen factor is added to obtain a sunscreen factor of approximately 4.

Traditional conservation agents such as for example methyl-p-hydroxybenzoat and/or acetyl-p-oxybenzoat are added  
25 during the final process in sufficient amounts.

The above formulation may be used for cosmetic purposes and to alleviate skin irritant conditions and solar dermatitis.

### 30 **Example 2            Gel formulation**

100 gram CLA 80 (Natural AS Oslo) is heated with 30 g Chitosan, Biopolymer L112 (Natural, Oslo) to 70°C with stirring for about half an hour. The complex formed is then allowed to slowly cool to 50°C.  
35 20 g A-vitamin palmitate (Roche) is heated to 55°C together with 10 g Chitosan, Biopolymer L 112 (Natural,Oslo) with stirring for about half an hour. The complex is subsequently cooled to 50°C.



- 20 g tocopherol acetate is heated to 55°C together with 10 g Chitosan, Biopolymer L 112 (Natural,Oslo) with stirring for about half an hour and 20 g tocopherol is heated to 55°C together with 10 g Chitosan, Biopolymer L 112 (Natural,Oslo) with stirring for about half an hour. The complexes are subsequently cooled to 50°C, and are then mixed into Carbomer (carboxy methyl cellulose) heated to 50°C, together with the CLA-chitosan-complex of 50°C. Water is then added and pH of the newly formed solution is adjusted with lactate or sodium bicarbonate to pH 5.0-5.5. The final volume is adjusted to 100 ml with water. The amounts of the ingredients are: chitosan 0.5 wt%, tocopherol acetate 0.2 wt%, tocopherol 0.05 wt% and CLA 2 wt% and Carbomer 0.3 wt%.

15

In the final formulation sunscreen factor as well as traditional conservation agent may be added in sufficient amounts.

- 20 The above gel can be used to treat atopic dermatitis and psoriasis eczema as well as eczema of different origins and severe solar dermatitis.

### Example 3 Cream formulation

25 Formulation for day cream (100 ml)

Ingredients	Amount
Arachidis oleum	13 ml
Emulsifier, non-ionic	6 g
Stearin	6 g
CLA	2 g
Chitosan	0.5 g
Vit A densatum Ph. Eur.	0.2 g
Methyl-p-hydroxybenzoate	0.1 g
Acetyl-p-oxybenzoate	0.1 g
Triethanolamine	100 mg
Resin	50 mg
Lactate until pH 4.5	
Tocopherol	100 mg

Distilled water	q.s.
Sun screen F6 (PABA)	3%

The formulation can be prepared in accordance with the above examples and is suitable for cosmetic use.

5 **Example 4 Cream formulation**

Formulation for nighth cream (100 ml)

Ingredients	Amount
Arachidis oleum	17.05 ml
Oleum soya	19.5 ml
Emulgator E 471 and E 472 c	6.2 g
CLA	2 g
Chitosan	0.5 g
Methyl-p-hydroxybenzoate	0.143 g
Acetyl-p-oxybenzoate	0.2 g
Vit A densatum Ph. Eur.	0.2
Tocopherol	100 mg
Lactate until pH 4.5	
Distilled water	q.s.

The formulation can be prepared in accordance with the above examples and is suitable for cosmetic use.

10

**Example 5 Effect on skin thickness and elasticity**

The formulation prepared in example 1 containing chitosan conjugated CLA was tested in a pilot study.

15 **Materials and methods**

The study was carried out as an open study in 20 healthy females aged between 40 and 60 years (mean 49.2 yrs) who applied the ointment on the right volar (protected part) of the right forearm. The left forearm was used as a control and was not treated. The total treatment period was 3 months and administration was bid (in the morning and in the evening) during the study period. The study was carried out in accordance with the revised Helsinki declaration. All subjects received information about the aim of the

study before inclusion and participate voluntarily in the study.

#### Measurements of skin thickness and skin elasticity

5 The measurements of skin thickness and skin elasticity were performed by ultrasound using Dermascan and Dermaflex instruments, respectively (Cortex Inc., Aarhus, Denmark). Measurements were carried out at baseline, after 1 months and after 3 months, by the same person on all three  
10 occasions and measurements were performed at the mid-region of the volar part of the forearm. All measurements were in triplicate and average values used for statistical evaluation.

#### Self-evaluation by the participants

At the same time as the objective measurements were carried out, participants made a self-evaluation of skin quality using visual analogue scales of 10 cm with end-points of "no change" and "very pronounced change". Subjects were  
20 asked to score the global change in skin quality by placing a mark on the line between the endpoints. The distance from the endpoint (0 cm) to the mark was used as the score for the subject.

#### Statistical methods

A significance level of 5% was used in the tests and two-tailed tests were applied. The one sample test was used analysing change over time within groups. Two-sample t-test  
30 were used to compare arms with regard to continuous variables.

#### RESULTS

The results from the skin thickness measurements are shown in Table 1. As can be seen from the table the ointment gave  
35 an increase in skin thickness of 51% as compared to no change for the untreated arm. This change is highly significant ( $p < 0.01$ ).

**Table 1:** Change in skin thickness (mm) after administration of the ointment and no treatment for 3 months in 20 females.

	Initially	After 1 month	After 3 months
Ointment Mean (SD)	0.89 (0.13)	1.10 (0.20)	1.35 (0.19)
No treatment Mean (SD)	0.90 (0.10)	0.91 (0.11)	0.89 (0.12)

- 5 The viscoelastic properties of the skin is shown in table 2.

**Table 2:** Change in skin elasticity (%) after administration of the ointment for 3 months in 20 females

	Initially	After 1 month	After 3 months
Ointment Mean (SD)	59.0 (8.0)	70.0 (7.9)	75.2 (8.5)
No treatment Mean (SD)	61.0 (7.5)	60.0 (8.0)	61.5 (8.1)

10

The results show that the elasticity is improved by 27% on the ointment treated arm while no change is observed on the control arm.

- 15 The self-evaluation shows impressing results. The average score was 7.9 cm. The participants felt that they got a smoother and more elastic skin. They also expressed that they were highly satisfied with the cosmetic properties of the ointment. The rapid penetration of the ointment into  
20 the skin was highly appreciated by the participants.

No tolerability problems were reported during the study. The tolerability was excellent. All participants would like to continue with the ointment.

25

The results from this study shows very good effects in improving skin thickness and elasticity. Compared to previous studies with  $\beta$ -cyclodextrin conjugated Vitamin A

esters (Thom E., *Skin treatment with two different galenical formulations of retinyl palmitate in humans*. J Appl Cosmetology 1993, 11; 71-76; Thom E., *Long-term effects after topical application of active retinyl palmitate*. J Appl Cosmetology 1994, 12; 45-50; and Thom E., *A comparative double-blind within subject study of the efficacy and tolerability of two different derivatives of Vitamin A on skin thickness and elasticity: retinoic acid and conjugated retinyl palmitate*. J Appl Cosmetology 1997, 15; 133 -138) the present results are better showing an average improvement in skin thickness and elasticity of 51% and 27%, respectively. The previous studies only showed an improvement of about 32% and 19%, respectively, using the same measuring devices. The average global score on the satisfaction of the present formulation is also impressive with an average final score of 7.9 cm.



**Claims**

1. Composition **characterised in** that it contains chitosan conjugated CLA (conjugated linoleic acid) and a chitosan conjugated Vitamin A or a  $\beta$ -cyclodextrin conjugated vitamin A, where the content of CLA is 0.1-99 wt%, the content of chitosan is 0.025-25 wt%, and the content of Vitamin A is 0.025-10 wt%.  
5
2. Composition according to claim 1, **characterised in** that it optionally contains chitosan conjugated vitamin E, sun protective factor, bovine colostrum concentrate and/or lactose.  
10
3. Composition according to claim 1 or 2, **characterised in** that the CLA contains cis-9-trans-11-linoleic acid (c9t11) and trans-10-cis-12-linoleic acid (t10c12).  
15
4. Composition according to any of the claims 1-3, **characterised in** that the CLA contains 0.1 - 90% of each isomer, preferably in a 50:50 relation.  
20
5. Composition according to any of the claims 1-4, **characterised in** that the CLA is CLA 80, CLA isomer c9t11 or CLA 80 isomer t10c12.  
25
6. Composition according to any of the presiding claims, **characterised in** that the amount of CLA in the composition in form of chitosan conjugated CLA preferably is 0.5 wt% to 70 wt% and most preferred 0.8 wt% to 40 wt%.  
30
7. Composition according to any of the presiding claims, **characterised in** that the chitosan has a molecular weight between 5,000 to 50,000.  
35
8. Composition according to any of the presiding claims, **characterised in** that the chitosan has a percent of deacetylation in the range of 70-95, preferably 87-90%.

9. Composition according to any of the presiding claims,  
**characterised in** that the chitosan polymer itself has a  
viscosity in the range of 120-169 mPas, preferably about  
140 mPas.
10. Composition according to any of the presiding claims,  
**characterised in** that the chitosan polymer is Chitosan  
Biopolymer L112.
11. Composition according to any of the presiding claims,  
**characterised in** that the ratio of CLA to chitosan in  
the chitosan conjugated CLA is in the range of 25 : 1 to  
1:2, preferably 4:1.
12. Composition according to any of the presiding claims,  
**characterised in** that the amount of chitosan in the  
composition in the form of chitosan conjugated CLA and  
chitosan conjugated vitamin A preferably is 0.1 wt% - 16  
wt% and most preferred 0.5 wt% - 10 wt%.
13. Composition according to any of the presiding claims,  
**characterised in** that the ratio of chitosan to vitamin A  
in the chitosan conjugated vitamin A is in the range of  
1:25 to 1:1.
14. Composition according to claim 2, **characterised in**  
that the bovien colostrum concentrate contains IgG in an  
amount of 70-85% of the total antibody content, IgA in  
an amount of about 15% of the total antibody content,  
IgM in an amount of 5-10% of the total antibody content,  
IgD in an amount of 0.2% of the total antibody content  
and IgE in an amount of 0.002% of the total antibody  
content, as well as IGF-1 in a concentration of about  
250 ng/kg colostrum concentrate.
15. Composition according to claim 2 and 14, **characterised**  
**in** that the amount of freeze-dried bovien colostrum

concentrate included in the composition is from 0.5 g up to 10 g per 100 g of the composition.

16. Composition according to claim 2, **characterised in**  
5 that the sun protective factor is between 1 and 30,  
preferably 4.
17. Composition according to any of the presiding claims,  
**characterised in** that the pH of the composition is  
10 between 2 and 8, preferably 5.5.
18. Process for preparation of a composition according to  
claim 1, **characterised in** that:  
- chitosan is heated together with CLA at 70°C for about  
15 half an hour, followed by cooling to about 50°,  
- chitosan is heated together with vitamin A at 55°C for  
about half an hour,  
- chitosan conjugated vitamin A and chitosan conjugated  
CLA are mixed at 50°C,  
20 - optionally the conjugates are mixed with a composition  
base at 50°C,  
- the pH of the composition is adjusted to a pH between  
2 and 8, preferably 5.5,  
- additional ingredients, if any, are added to the  
25 mixture.
19. Use of a composition according to any of the claims 1-  
17 for preparation of a topical composition.
- 30 20. Use of a composition according to any of the claims 1-  
17 for preparation of a cosmetic composition.
21. Use of a composition according to any of the claims 1-  
17 for preparation of a pharmaceutical composition.
- 35 22. Use of a composition according to any of the claims 1-  
17 for preparation of a pharmaceutical composition for  
treatment of atypical dermatitis, psoriasis eczema as

well as eczema of different origins and solar dermatitis.

5 23. Use of a composition according to any of the claims 1-17 to improve the skin thickness and elasticity.

10 24. Method for improving the skin thickness and the skin elasticity characterized by applying a sufficiently amount of a composition according to any of the claims 1-17 on the skin of a human or animal subject.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/NO 01/00437

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 7/48, A61K 31/201, A61K 31/202, A61K 31/07, A61K 47/36, A61P 17/00  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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P,X	J. Appl. Cosmetol, Volume 19, No. 2, April/June 2001, E. Thom et al: "The effect of a new skin ointment on skin thickness and elasticity", pages 51-57 --	1-24
X	WO 9926588 A2 (NATURAL NUTRITION LTD.), 3 June 1999 (03.06.99), page 1, line 8 - line 16; page 7, line 19 - page 9, line 4; page 10, line 33 - line 36, page 14, line 24 - page 15, line 16, page 17, line 20 - line 35, the claims --	1-24

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier application or patent but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art  
 "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

12 February 2002

20-02-2002

Name and mailing address of the ISA/  
 Swedish Patent Office  
 Box 5055, S-102 42 STOCKHOLM  
 Facsimile No. +46 8 666 02 86

Authorized officer  
 GERD STRANDELL/BS  
 Telephone No. +46 8 782 25 00



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/NO 01/00437

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5057542 A (LEUBA ET AL), 15 October 1991 (15.10.91) --	1-24

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International application No.

PCT/NO 01/00437

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	<p>WO 0108650 A1 (UNILEVER PLC), 8 February 2001  (08.02.01), page 15, line 25 - page 16, line 5,  page 21, Table 2, page 23, Table 3, page 39, line  21 - page 40, line 20, claims 1-7,16-18</p> <p>--  -----</p>	1-24

## INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.

PCT/NO 01/00437

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